Association Between Immune-Related Adverse Events During Anti–PD-1 Therapy and Tumor Mutational Burden

Bomze, David ; Hasan Ali, Omar ; Bate, Andrew ; Flatz, Lukas

Abstract: Immune checkpoint inhibitors (ICIs) that target the programmed death 1 receptor (anti–programmed cell death 1 [PD-1] therapy) have ushered in a new era of cancer therapy. However, their application has been curtailed by serious immune-related adverse events (irAEs), such as colitis, pneumonitis, and myocarditis, that remain largely unpredictable. Although the use of tumor mutational burden (TMB) as a biomarker for expected therapy response has been advocated,1 a similar parameter for irAEs is lacking. In an attempt to fill this clinically relevant knowledge gap, we investigated the association between irAEs reported during anti–PD-1 therapy and TMB by comparing large-scale surveillance data of irAEs with the median TMB across multiple cancer types. Methods We retrieved postmarketing data of adverse events from the US Food and Drug Administration Adverse Event Reporting System (FAERS) from July 1, 2014, to March 31, 2019. According to the ethics committee policy of the EKOS (Ethikkommission Ostschweiz, Switzerland), this study was exempt from ethical review because all analyzed datasets are deidentified and publicly available. We considered only reports for which the anti–PD-1 agents nivolumab or pembrolizumab were the suspected cause of adverse events. Anti–PD-1 and anti-cytotoxic T-lymphocyte–associated protein 4 combination treatment was excluded. Closely related indications were aggregated to unified terms; for example, “malignant melanoma” was aggregated to “melanoma.” To limit our analysis to irAEs, we filtered terms to match broadly accepted diagnoses that were outlined in peer-reviewed irAE management guidelines. The median TMB in tumor tissue was obtained from previously published comprehensive genomic profiling.2,3 Lastly, we only considered cancers for which there were at least 100 cases of adverse events during anti–PD-1 therapy reported in FAERS. To assess the risk of a patient developing any irAE, we estimated reporting odds ratios (RORs) by comparing the odds of reporting these irAEs rather than others for the anti–PD-1 agents with the odds for all other drugs in the database, which represents standard practice for quantitative analyses of data in FAERS and similar databases.4 Results Our search strategy identified a total of 47 304 adverse events (AEs) in 16 397 patients reported as treated with anti–PD-1 monotherapy for 19 different cancer types. Of these patients, 3661 had at least 1 irAE (22.3%; 95% CI, 21.7-23.0). The comparator group comprised 16 411 749 AE reports from 5 160 064 patients. Our analysis revealed a significant positive correlation between the ROR of reporting an irAE during anti–PD-1 therapy and the corresponding TMB across multiple cancer types, with a higher ROR of irAE associated with a higher median number of coding somatic mutations per megabase of DNA (Figure; Pearson correlation coefficient $R = 0.704$; $P < .001$). The correlation coefficient suggests that 50% of the differences in the irAE risk across cancer types may be attributed to the TMB. Discussion Our analysis indicates that cancers with a high TMB, such as melanoma and non–small cell lung cancer, are associated with a higher irAE ROR during anti–PD-1 therapy, strongly suggesting that these cancers are associated with a higher risk of irAEs than cancers with a low TMB. A possible explanation for this finding may be the different neoantigenic load across cancer types. Additionally, studies have shown that T cells that react against a neoantigen can crossreact against the corresponding wild-type protein.5 Another contributing mechanism may be antigen spreading, where tumor cell death releases antigens, including neoantigens, that prime lymphocytes against the wild-type antigens in healthy tissue. Given the results of the analysis, we propose that the association between irAEs and improved response to anti–PD-1 treatment are linked via an underlying

neoantigenic potential that stems from a high TMB. A limitation of the study is the use of spontaneous reports for indirectly measuring the risk of irAE. Furthermore, patients with cancers with a high TMB may receive a longer course of anti–PD-1 treatment. However, most irAEs reported during anti–PD-1 therapy develop within the first few weeks of treatment.6 This finding suggests that therapy duration is unlikely to influence the statistical outcome. In conclusion, a high TMB may be a useful biomarker for assessing patients' risk of irAEs during anti–PD-1 therapy, which has particular relevance for vulnerable patient groups.

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Letters

RESEARCH LETTER

Association Between Immune-Related Adverse Events During Anti–PD-1 Therapy and Tumor Mutational Burden

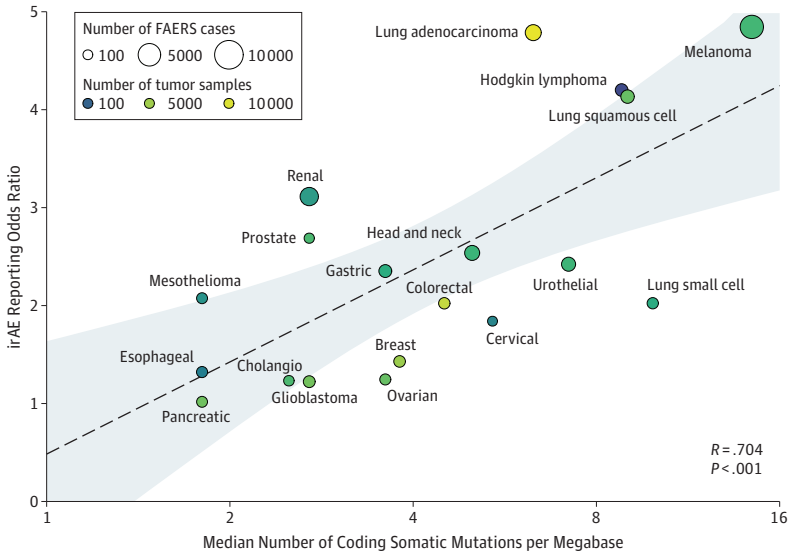
Immune checkpoint inhibitors (ICIs) that target the programmed death 1 receptor (anti-programmed cell death 1 [PD-1] therapy) have ushered in a new era of cancer therapy. However, their application has been curtailed by serious immune-related adverse events (irAEs), such as colitis, pneumonitis, and myocarditis, that remain largely unpredictable. Although the use of tumor mutational burden (TMB) as a biomarker for expected therapy response has been advocated,[1] a similar parameter for irAEs is lacking. In an attempt to fill this clinically relevant knowledge gap, we investigated the association between irAEs reported during anti-PD-1 therapy and TMB by comparing large-scale surveillance data of irAEs with the median TMB across multiple cancer types.

Related article

Methods | We retrieved postmarketing data of adverse events from the US Food and Drug Administration Adverse Event Reporting System (FAERS) from July 1, 2014, to March 31, 2019. According to the ethics committee policy of the EKOS (Ethikkommission Ostschweiz, Switzerland), this study was exempt from ethical review because all analyzed datasets are deidentified and publicly available. We considered only reports for which the anti-PD-1 agents nivolumab or pembrolizumab were the suspected cause of adverse events. Anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 combination treatment was excluded. Closely related indications were aggregated to unified terms; for example, "malignant melanoma" was aggregated to "melanoma." To limit our analysis to irAEs, we filtered terms to match broadly accepted diagnoses that were outlined in peer-reviewed irAE management guidelines. The median TMB in tumor tissue was obtained from previously published comprehensive genomic profiling.[2,3] Lastly, we only considered cancers for which there were at least 100 cases of adverse events during anti-PD-1 therapy reported in FAERS. To assess the risk of a patient developing any irAE, we estimated reporting odds ratios (RORs) by comparing the odds of reporting these irAEs rather than others for the anti-PD-1 agents with the odds for all other drugs in the database, which represents standard practice for quantitative analyses of data in FAERS and similar databases.[4]

Results | Our search strategy identified a total of 47 304 adverse events (AEs) in 16 397 patients reported as treated with anti-PD-1 monotherapy for 19 different cancer types. Of these patients, 3661 had at least 1 irAE (22.3%; 95% CI, 21.7-23.0). The comparator group comprised 16 411 749 AE reports from 5 160 064 patients. Our analysis revealed a significant positive correlation between the ROR of reporting an irAE during anti-PD-1 therapy and the corresponding TMB across multiple cancer types, with a higher ROR of irAE associated with a higher median number of coding somatic mutations per megabase of DNA (**Figure**; Pearson correlation coefficient

Figure. Association of Tumor Mutational Burden With Immune-Related Adverse Events During Anti–PD-1 Therapy Across Multiple Cancers



The x-axis indicates the tumor mutational burden (TMB)—defined as the median number of coding somatic mutations per megabase of DNA—across 19 cancer types. Data on the x-axis are presented on a logarithmic scale. The y-axis shows the reporting odds ratio of any immune-related adverse event (irAE) across cancer types, calculated using data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database. The dashed line represents the 95% CI of the linear fit. Circle size represents the total number of FAERS cases for each cancer type, and the color indicates the total number of tumor samples used to measure TMB for each cancer type.

$R = 0.704$; $P < .001$). The correlation coefficient suggests that 50% of the differences in the irAE risk across cancer types may be attributed to the TMB.

Discussion | Our analysis indicates that cancers with a high TMB, such as melanoma and non–small cell lung cancer, are associated with a higher irAE ROR during anti–PD-1 therapy, strongly suggesting that these cancers are associated with a higher risk of irAEs than cancers with a low TMB. A possible explanation for this finding may be the different neoantigenic load across cancer types. Additionally, studies have shown that T cells that react against a neoantigen can cross-react against the corresponding wild-type protein.[5] Another contributing mechanism may be antigen spreading, where tumor cell death releases antigens, including neoantigens, that prime lymphocytes against the wild-type antigens in healthy tissue. Given the results of the analysis, we propose that the association between irAEs and improved response to anti–PD-1 treatment are linked via an underlying neoantigenic potential that stems from a high TMB. A limitation of the study is the use of spontaneous reports for indirectly measuring the risk of irAE. Furthermore, patients with cancers with a high TMB may receive a longer course of anti–PD-1 treatment. However, most irAEs reported during anti–PD-1 therapy develop within the first few weeks of treatment.[6] This finding suggests that therapy duration is unlikely to influence the statistical outcome. In conclusion, a high TMB may be a useful biomarker for assessing patients' risk of irAEs during anti–PD-1 therapy, which has particular relevance for vulnerable patient groups.

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Study concept and design: Bomze, Hasan Ali, Flatz.
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Drafting of the manuscript: Bomze, Hasan Ali, Bate.
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Statistical analysis: Bomze, Bate.
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Study supervision: Bate, Flatz.

Conflict of Interest Disclosures: Mr Bate is an employee of Pfizer; this work was conducted outside his employment, and the contents herein represent his personal opinions. Dr Flatz reports grants from the Swiss National Science Foundation, Swiss Cancer League, Hookipa Pharma, Krebsliga Schweiz, and Novartis Foundation as well as an advisory role for Novartis and Bristol-Myers Squibb. No other disclosures were reported.

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